

March 23, 2008

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450



10 557 333

I, Leslie Binshyang Song, hereby declare that United States Patent Application 20070219583, Kind Code A1, with the Applicants: Eduardo Chi Sing, Mark Ashby, Tin Tran, and Richard Greff is exactly the copy of my hemostat ingredients of my United States Patent No: US 6,783,774 B1 and is not patentable therefor, because all the chitosan and gelatin of claims 1-32 of their patent application (Exhibit 1) are excipients, all of which are excipients of my hemostat Patent claims 1-20 (Exhibit 2). The said excipients are chitosan (cellulose derivative), cellulose, gelatin etc. (Handbook of Pharmaceutical Excipients fourth Edition 2003 edited by Raymond C Rowe et al (Exhibit 3, Pages v & vi, 112 & 132 & 252) and Exhibits 4, Page 2 of 4). Chitosan is Poly-D-glucosamine ([www.epa.gov](http://www.epa.gov) Exhibit 5, Page 1 of 2), which is my cellulose derivative of my excipients in which the hydroxyl group at glucose carbon 2 is substituted by amino group (Exhibit 6, Page 1 of 2) thereof. Apparently, Gelatin and Chitosan are excipients of my hemostat Patent claims.

The claim 29 of Patent Application 20070219583, the water is added and hydrolysis of Poly-D-glucosamine leads to Poly-glucose which is my cellulose. Anyway, cellulose, cellulose derivative (chitosan) and gelatin are the excipients of my hemostat patent claims.

I wish to express my great appreciation to you for your assistance with this urgent matter.

Respectfully submitted,

Leslie Binshyang Song, M.A., M.D.

*Exhibit 1***US PATENT & TRADEMARK OFFICE**  
**PATENT APPLICATION FULL TEXT AND IMAGE DATABASE**

( 42 of 438 )

**United States Patent Application****20070219583****Kind Code****A1****Sing; Eduardo Chi ; et al.****September 20, 2007****System And Method For Facilitating Hemostatis With An Absorbable Sponge****Abstract**

The present invention provides for a method and apparatus to provide hemostasis at a blood vessel puncture site, having a hemostasis material and a clot formation accelerator, wherein said clot formation accelerator is substantially dispersed throughout said hemostasis material.

**Inventors:** **Sing; Eduardo Chi;** *(Dana Point, CA)* ; **Ashby; Mark;** *(Laguna Niguel, CA)* ; **Tran; Tin;** *(Anaheim, CA)* ; **Greff; Richard;** *(St. Pete Beach, FL)*

**Correspondence Name and Address:** **MILLER, MATTHIAS & HULL**  
**ONE NORTH FRANKLIN STREET**  
**SUITE 2350**  
**CHICAGO**  
**IL**  
**60606**  
**US**

**Serial No.:** **557333****Series Code:** **10****Filed:** **June 14, 2004****PCT Filed:** **June 14, 2004****PCT NO:** **PCT/US04/18707****371 Date:** **November 20, 2006****U.S. Current Class:****606/213****U.S. Class at Publication:****606/213****Intern'l Class:****A61B 17/03 20060101 A61B017/03****Claims**

1. An apparatus to provide *hemostasis* at a blood vessel puncture site, comprising: a *hemostasis* material; and a clot formation accelerator, wherein said clot formation accelerator is substantially dispersed throughout said *hemostasis* material.
2. The apparatus of claim 1 wherein said clot formation accelerator is a clot agglomeration.
3. The apparatus of claim 1 wherein said clot formation accelerator is Chitosan.
4. The apparatus of claim 1 wherein said clot formation accelerator is a thrombogenic agent.
5. The apparatus of claim 4 further comprising a polysaccharide.
6. The apparatus of claim 6 wherein said polysaccharide is Chitosan.
7. An apparatus to provide *hemostasis* at a blood vessel puncture site, comprising: a *hemostasis* material; a clot formation accelerator; and a polysaccharide, wherein said clot formation accelerator and said polysaccharide are substantially dispersed throughout said *hemostasis* material.
8. The apparatus of claim 7 further comprising a cross-linking agent.
9. The apparatus of claim 7 wherein said clot formation accelerator is a thrombogenic agent.
10. The apparatus of claim 7 wherein said polysaccharide is Chitosan.
11. An apparatus to provide *hemostasis* at a blood vessel puncture site, comprising: a *hemostasis* material; a cross-linking agent; a polysaccharide; and a clot formation accelerator, wherein said cross-linking agent, said clot formation accelerator, and said polysaccharide are substantially dispersed throughout said *hemostasis* material.
12. The apparatus of claim 11 wherein said clot formation accelerator is a thrombogenic agent.
13. The apparatus of claim 11 wherein said polysaccharide is Chitosan.
14. The apparatus of claim 11 wherein said cross-linking agent is a formaldehyde.
15. A method for forming a clot formation accelerator loaded *hemostasis* material, comprising: heating gelatin granules in water; adding a cross-linking agent; mixing a clot formation accelerator to the cross-linking agent and heated gelatin solution; and adding air to form a gelatin foam *hemostasis* material matrix, wherein said clot formation accelerator is substantially dispersed throughout said *hemostasis* material.
16. The method of claim 15 wherein said dissolving further comprises adding a polysaccharide.
17. The method of claim 16 wherein said polysaccharide is Chitosan.
18. The method of claim 16 wherein the clot formation accelerator is a thrombogenic agent.
19. The method of claim 15 further comprising drying said gelatin foam *hemostasis* material matrix above a freezing point temperature.

20. A method for forming a clot formation accelerator loaded *hemostasis* material, comprising: heating gelatin granules in water; adding a cross-linking agent; mixing a clot formation accelerator to the cross-linking agent and heated gelatin solution; and drying said clot formation accelerator mixture at a temperature above a freezing point temperature to form said *hemostasis* material, wherein said clot formation accelerator is substantially dispersed throughout said *hemostasis* material.
21. The method of claim 20 wherein said heating further comprises adding a polysaccharide.
22. The method of claim 21 wherein said polysaccharide is Chitosan.
23. The method of claim 21 wherein the clot formation accelerator is a thrombogenic agent.
24. An apparatus for forming a clot formation accelerator loaded *hemostasis* material, comprising: means for heating gelatin granules in water; means for adding a cross-linking agent; means for mixing a clot formation accelerator to the cross-linking agent and heated gelatin solution; and means for adding air to form a gelatin foam *hemostasis* material matrix, wherein said clot formation accelerator is substantially dispersed throughout said *hemostasis* material.
25. The apparatus of claim 24 wherein said means for dissolving further comprises adding a polysaccharide.
26. The apparatus of claim 25 wherein said polysaccharide is Chitosan.
27. The apparatus of claim 25 wherein the clot formation accelerator is a thrombogenic agent.
28. The apparatus of claim 24 further comprising means for drying said gelatin foam *hemostasis* material matrix above a freezing point temperature.
29. An apparatus for forming a clot formation accelerator loaded *hemostasis* material, comprising: means for heating gelatin granules in water; means for adding a cross-linking agent; means for mixing a clot formation accelerator to the cross-linking agent and heated gelatin solution; and means for drying said clot formation accelerator mixture at a temperature above a freezing point temperature to form said *hemostasis* material, wherein said clot formation accelerator is substantially dispersed throughout said *hemostasis* material.
30. The apparatus of claim 29 wherein said means for heating further comprises adding a polysaccharide.
31. The apparatus of claim 30 wherein said polysaccharide is Chitosan.
32. The apparatus of claim 30 wherein the clot formation accelerator is a thrombogenic agent.

---

### *Description*

---

### CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claim priority to Co-pending U.S. patent application Ser. No. 60/478,307, filed Jun. 12, 2003, by inventors Eduardo Chi Sing, Mark Ashby, and Tin Tran, entitled "Improved System

# Handbook of Pharmaceutical Excipients

Fourth Edition

Edited by  
Raymond C Rowe, Paul J Sheskey  
and Paul J Weller



Pharmaceutical Press



APhA  
American  
Pharmaceutical  
Association

Exhibit 3

# Handbook of Pharmaceutical Excipients

FOURTH EDITION

Edited by

**Raymond C Rowe**

BPharm, PhD, DSc, FRPharmS, CChem, FRSC, CPhys, MInstP

Senior Principal Scientist

AstraZeneca

Macclesfield, UK

**Paul J Sheskey**

BSc, RPh

Technical Service Leader

Water Soluble Polymers R&D

The Dow Chemical Company

Midland

MI, USA

**Paul J Weller**

BSc, MSc, CChem, MRSC

Publisher - Science and Practice

Royal Pharmaceutical Society of Great Britain

London, UK

**(PP)<sub>h</sub>**  
London • Chicago **Pharmaceutical Press**

  
**APhA**  
American  
Pharmaceutical  
Association

PS 201  
145  
H34  
2003

**Published by the Pharmaceutical Press**

Publications division of the Royal Pharmaceutical Society of Great Britain

1 Lambeth High Street, London SE1 7JN, UK

100 South Atkinson Road, Suite 206, Grayslake, IL 60030-7820, USA

**and the American Pharmaceutical Association**

2215 Constitution Avenue NW, Washington, DC 20037-2985, USA

© Pharmaceutical Press and American Pharmaceutical Association 2003

**(PP)** is a trade mark of Pharmaceutical Press

First edition published 1986

Second edition published 1994

Third edition published 2000

Fourth edition published 2003

Text design by Barker Hilsdon, Lyme Regis

Typeset by Bibliocraft Ltd, Dundee

Printed in Great Britain by The Bath Press, Bath

ISBN 0 85369 472 9 (UK)

ISBN 1 58212 022 6 (USA)

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder.

The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

A catalogue record for this book is available from the British Library

**Library of Congress Cataloging-in-Publication Data**

Handbook of pharmaceutical excipients.—4th ed. / edited by Raymond C.

Rowe, Paul J. Sheskey, Paul J. Weller.

p. ; cm.

Includes bibliographical references and index.

ISBN 1-58212-022-6 (alk. paper) — ISBN 0-85369-472-9 (alk. paper)

1. Excipients—Handbooks, manuals, etc.

[DNLM: 1. Excipients—Handbooks. QV 735 H236 2003] I. Rowe, Raymond

C. II. Sheskey, Paul J. III. Weller, Paul J.

RS201.E87H36 2003

615'.19—dc21

2003002641

# Contents

International Steering Committee	ix
Editorial Staff	ix
Contributors	x
About the Editors	xiii
New Monographs	xiv
Related Substances	xv
Preface	xvii
Acknowledgments	xix
Notice to Readers	xix
Bibliography	xx
Abbreviations	xxi
Units of Measurement	xxii

## Monographs

Acacia	1
Acesulfame Potassium	3
Acetic Acid, Glacial	5
Acetyltributyl Citrate	7
Acetyltriethyl Citrate	9
Albumin	11
Alcohol	13
Alginic Acid	16
Aliphatic Polyesters	19
Alitame	23
Almond Oil	25
Alpha Tocopherol	27
Ammonia Solution	30
Ascorbic Acid	32
Ascorbyl Palmitate	35
Aspartame	37
Attapulgate	40
Bentonite	42
Benzalkonium Chloride	45
Benzethonium Chloride	48
Benzoic Acid	50
Benzyl Alcohol	53

Benzyl Benzoate	56
Bronopol	58
Butylated Hydroxyanisole	61
Butylated Hydroxytoluene	63
Butylparaben	65
Calcium Carbonate	68
Calcium Phosphate, Dibasic Anhydrous	72
Calcium Phosphate, Dibasic Dihydrate	74
Calcium Phosphate, Tribasic	78
Calcium Stearate	80
Calcium Sulfate	83
Canola Oil	86
Carbomer	89
Carbon Dioxide	93
Carboxymethylcellulose Calcium	95
Carboxymethylcellulose Sodium	97
Carrageenan	101
Castor Oil	104
Castor Oil, Hydrogenated	106
Cellulose, Microcrystalline	108
Cellulose, Powdered	112
Cellulose, Silicified Microcrystalline	115
Cellulose Acetate	117
Cellulose Acetate Phthalate	120
Ceratonin	123
Cetostearyl Alcohol	125
Cetrimide	127
Cetyl Alcohol	130
Chitosan	132
Chlorhexidine	136
Chlorobutanol	141
Chlorocresol	144
Chlorodifluoroethane (HCFC)	147
Chlorofluorocarbons (CFC)	149
Chloroxylonol	153
Cholesterol	155
Citric Acid Monohydrate	158



Colloidal Silicon Dioxide	161	Hydrocarbons (HC)	278
Coloring Agents	165	Hydrochloric Acid	281
Corn Oil	174	Hydroxyethyl Cellulose	283
Cottonseed Oil	176	Hydroxyethylmethyl Cellulose	287
Cresol	178	Hydroxypropyl Cellulose	289
Croscarmellose Sodium	181	Hydroxypropyl Cellulose, Low-substituted	294
Crospovidone	184	Hypromellose	297
Cyclodextrins	186	Hypromellose Phthalate	301
Cyclomethicone	191	Imidurea	306
Denatonium Benzoate	193	Isopropyl Alcohol	309
Dextrates	195	Isopropyl Myristate	312
Dextrin	197	Isopropyl Palmitate	314
Dextrose	200	Kaolin	316
Dibutyl Phthalate	203	Lactic Acid	319
Dibutyl Sebacate	205	Lactitol	321
Diethanolamine	207	Lactose	323
Diethyl Phthalate	209	Lanolin	333
Difluoroethane (HFC)	211	Lanolin, Hydrous	336
Dimethicone	213	Lanolin Alcohols	338
Dimethyl Ether	215	Lecithin	340
Dimethyl Phthalate	217	Magnesium Aluminum Silicate	343
Dimethyl Sulfoxide	219	Magnesium Carbonate	347
Docusate Sodium	222	Magnesium Oxide	350
Edetic Acid	225	Magnesium Silicate	352
Ethyl Acetate	229	Magnesium Stearate	354
Ethyl Maltol	231	Magnesium Trisilicate	358
Ethyl Oleate	233	Malic Acid	360
Ethyl Vanillin	235	Maltitol	362
Ethylcellulose	237	Maltitol Solution	364
Ethylene Glycol Palmitostearate	242	Maltodextrin	366
Ethylparaben	244	Maltol	369
Fructose	247	Maltose	371
Fumaric Acid	250	Mannitol	373
Gelatin	252	Medium-chain Triglycerides	378
Glucose, Liquid	255	Meglumine	381
Glycerin	257	Menthol	383
Glyceryl Behenate	260	Methylcellulose	386
Glyceryl Monooleate	262	Methylparaben	390
Glyceryl Monostearate	264	Mineral Oil	395
Glyceryl Palmitostearate	267	Mineral Oil, Light	398
Glycofurol	269	Mineral Oil and Lanolin Alcohols	400
Guar Gum	271	Monoethanolamine	402
Heptafluoropropane (HFC)	274	Monosodium Glutamate	404
Hexetidine	276	Monothioglycerol	406

# Cellulose, Powdered

## 1 Nonproprietary Names

BP: Powdered cellulose  
JP: Powdered cellulose  
PhEur: Cellulosi pulvis  
USPNF: Powdered cellulose

## 2 Synonyms

Arbocel; E460; Elcema; Sanacel; Solka-Floc.

## 3 Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

## 4 Empirical Formula

$(C_6H_{10}O_5)_n$

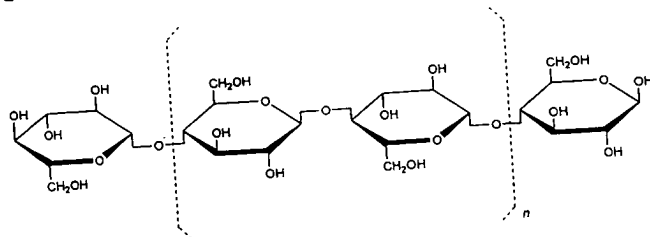
where  $n \approx 500$ .

Since cellulose is derived from a natural polymer, it has variable chain length and thus variable molecular weight. See also Sections 8 and 13.

## Molecular Weight

$\approx 243\,000$

## 5 Structural Formula



## 6 Functional Category

Adsorbent; glidant; suspending agent; tablet and capsule diluent; tablet disintegrant.

## 7 Applications in Pharmaceutical Formulation or Technology

Powdered cellulose is used as a tablet diluent and a hard gelatin capsule filler; see Table I. In both contexts it acts as a bulking agent to increase the physical size of the dosage form for formulations containing a small amount of active substance.

Powdered cellulose has acceptable compression properties, although its flow properties are poor. However, low-crystallinity powdered cellulose has exhibited properties that are different from standard powdered cellulose materials, and has shown potential as a direct-compression excipient.<sup>(1)</sup>

In soft gelatin capsules, powdered cellulose may be used to reduce the sedimentation rate of oily suspension fills. It is also used as the powder base material of powder dosage forms, and as a suspending agent in aqueous suspensions for peroral delivery. It may also be used to reduce sedimentation during the manufacture of suppositories.

Powdered cellulose has been investigated as an alternative to microcrystalline cellulose as an agent to assist the manufacture of pellets by extrusion/spheronization.<sup>(2)</sup>

Powdered cellulose is also used widely in cosmetics and food products.

Table I: Uses of powdered cellulose.

Use	Concentration (%)
Capsule filler	0-100
Tablet binder	5-25
Tablet disintegrant	5-15
Tablet glidant	1-2

## 8 Description

Powdered cellulose occurs as a white or almost white, odorless and tasteless powder of various particle sizes, ranging from a free-flowing fine or granular dense powder, to a coarse, fluffy, nonflowing material.

## 9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for powdered cellulose.

Test	JP 2001	PhEur 2002 (Suppl 4.2)	USPNF 20
Identification	+	+	+
Characters	+	+	—
Microbial limits			
Aerobic	$\leq 1000/g$	$\leq 1000/g$	$\leq 1000/g$
Fungi and yeast	$\leq 100/g$	$\leq 100/g$	—
Degree of polymerization	—	$\geq 440$	—
pH (10% w/w suspension)	5.0-7.5	5.0-7.5	+
Loss on drying	$\leq 6.0\%$	$\leq 6.5\%$	$\leq 6.0\%$
Residue on ignition	$\leq 0.3\%$	$\leq 0.3\%$	$\leq 0.3\%$
Solubility	—	+	—
Ether-soluble substances	$\leq 0.15\%$	$\leq 0.15\%$	$\leq 0.15\%$
Water-soluble substances	$\leq 1.5\%$	$\leq 1.5\%$	$\leq 1.5\%$
Heavy metals	$\leq 10\text{ ppm}$	$\leq 10\text{ ppm}$	$\leq 0.001\%$
Organic volatile impurities	—	—	+
Starch	—	+	—

## 10 Typical Properties

Angle of repose:

$< 62^\circ$  for Arbocel M80

$< 49^\circ$  for Arbocel P 290

$< 36^\circ$  for Arbocel A 300 (J. Rettenmaier and Söhne)

Density (bulk):  $0.139\text{--}0.391\text{ g/cm}^3$ , depending on the source.

Density (tapped):  $0.210\text{--}0.481\text{ g/cm}^3$ , depending on the source.

Density (true):  $1.5\text{ g/cm}^3$

# Chitosan

## 1 Nonproprietary Names

BP: Chitosan hydrochloride

PhEur: Chitosani hydrochloridum

## 2 Synonyms

2-Amino-2-deoxy-(1,4)- $\beta$ -D-glucopyranan; deacetylated chitin; deacetylchitin;  $\beta$ -1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4- $\beta$ -D-glucopyranosamine).

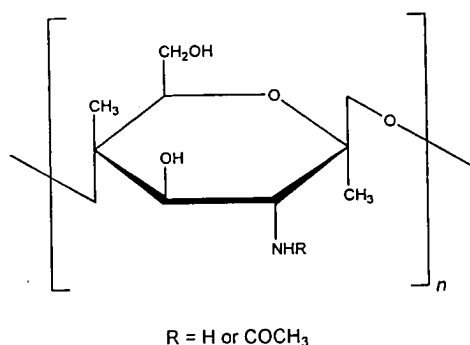
## 3 Chemical Name and CAS Registry Number

Poly- $\beta$ -(1,4)-2-Amino-2-deoxy-D-glucose [9012-76-4]

## 4 Empirical Formula      Molecular Weight

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition. A clear nomenclature with respect to the different degrees of *N*-deacetylation between chitin and chitosan has not been defined<sup>(1-3)</sup> and chitosan is not one chemical entity but varies in composition depending on the manufacturer. In essence, chitosan is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. Chitosan is commercially available in several types and grades that vary in molecular weight between 10 000 and 1 000 000, and vary in degree of deacetylation and viscosity.<sup>(4)</sup>

## 5 Structural Formula



## 6 Functional Category

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity-increasing agent.

## 7 Applications in Pharmaceutical Formulation or Technology

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies.<sup>(3,5-8)</sup> These include controlled drug delivery applications,<sup>(9-14)</sup> use as a component of mucoadhesive dosage forms,<sup>(15,16)</sup> rapid release dosage forms,<sup>(17,18)</sup> improved peptide delivery,<sup>(19,20)</sup> colonic drug delivery systems,<sup>(21,22)</sup> and use for gene delivery.<sup>(23)</sup> Chitosan has been processed into several pharmaceutical forms including gels,<sup>(24,25)</sup> films,<sup>(11,12,26,27)</sup> beads,<sup>(28,29)</sup> microspheres,<sup>(30,31)</sup> tablets,<sup>(32,33)</sup> and coatings for liposomes.<sup>(34)</sup> Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying,<sup>(15,16)</sup> coacervation,<sup>(35)</sup> direct compression,<sup>(32)</sup> and conventional granulation processes.<sup>(36)</sup>

## 8 Description

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fibre formation is quite common during precipitation and the chitosan may look 'cottonlike.'

## 9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for chitosan.

Test	PhEur 2002
Identification	+
Characters	+
Appearance of solution	+
Matter insoluble in water	$\leq 0.5\%$
pH (1% w/v solution)	4.0–6.0
Viscosity	+
Degree of deacetylation	+
Chlorides	10.0–20.0%
Heavy metals	$\leq 40$ ppm
Loss on drying	$\leq 10\%$
Sulfated ash	$\leq 1.0\%$

## 10 Typical Properties

Chitosan is a cationic polyamine with a high charge density at pH < 6.5 (and so adheres to negatively charged surfaces and chelates metal ions). It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation).<sup>(7)</sup> The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations.

# Gelatin

## 1 Nonproprietary Names

BP: Gelatin  
JP: Gelatin  
PhEur: Gelatina  
USPNF: Gelatin

## 2 Synonyms

Byco; Cryogel; gelatine; Instagel; Solugel.

## 3 Chemical Name and CAS Registry Number

Gelatin [9000-70-8]

## 4 Empirical Formula Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may also be a mixture of both types.

The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15 000–250 000.

The JP 2001 also includes a monograph for purified gelatin.

## 5 Structural Formula

See Section 4.

## 6 Functional Category

Coating agent; film-former; gelling agent; suspending agent; tablet binder; viscosity-increasing agent.

## 7 Applications in Pharmaceutical Formulation or Technology

Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system,<sup>(1)</sup> although it is most frequently used to form either hard or soft gelatin capsules.<sup>(2-4)</sup>

Gelatin capsules are unit-dosage forms that are filled with an active drug and are generally designed for oral administration. Although gelatin is poorly soluble in cold water, a gelatin capsule will swell in gastric fluid to rapidly release its contents.

Hard capsules are manufactured in two pieces by dipping stainless steel pins into a gelatin solution, which is distributed evenly around the pin. The gelatin is then set with a blast of chilled air and dried to remove moisture. The capsule halves are then removed, trimmed and filled before they are joined and closed with a tamper-evident seal. The USPNF 20 permits gelatin that is used to produce hard capsules to contain various coloring agents, antimicrobial preservatives, and sodium lauryl sulfate. Manufacturers may also add a hardening agent, such as sucrose, to hard gelatin capsules. Capsules varying in size from 0.13 to 1.37 mL volume are commercially available.

Soft gelatin capsules are formed from an aqueous gelatin solution that contains a plasticizer such as glycerin or sorbitol. Two soft gelatin strips are formed that run between suitable dies. As the dies meet, capsules are formed by injecting the

filling material, followed by the capsule halves being sealed together.

Gelatin is also used for the microencapsulation of drugs, where the active drug is sealed inside a micro-sized capsule or beadlet, which may then be handled as a powder. The first microencapsulated drugs (beadlets) were fish oils and oily vitamins in gelatin beadlets prepared by an emulsion process.

Low-molecular-weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs.<sup>(5)</sup> Other uses of gelatin include the preparation of pastes, pastilles, pessaries, and suppositories. In addition, it is used as a tablet binder and coating agent, and as a viscosity-increasing agent for solutions and semisolids.

Therapeutically, gelatin has been used in the preparation of wound dressings<sup>(6)</sup> and has been used as a plasma substitute, although anaphylactoid reactions have been reported in the latter application.<sup>(7)</sup> Absorbable gelatin is available as sterile film, ophthalmic film, sterile sponge, sterile compressed sponge, and sterile powder from sponge. Gelatin sponge has hemostatic properties.

Gelatin is also widely used in food products and photographic emulsions.

## 8 Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless and is available as translucent sheets and granules, or as a powder.

## 9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for gelatin.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Microbial contamination	—	≤ 1000/g	+
Residue on ignition	≤ 2.0%	≤ 2.0%	≤ 2.0%
Loss on drying	≤ 15.0%	≤ 15.0%	—
Odor and water-insoluble substances	—	—	+
Isoelectric point	+	+	—
Type A	7.0–9.0	6.3–9.2	—
Type B	4.5–5.0	4.7–9.2	—
Acidity or alkalinity	—	+	—
Clarity and color of solution	—	+	—
Sulfur dioxide	—	≤ 200 ppm	≤ 0.15%
Sulfite	+	—	≤ 0.8 ppm
Arsenic	≤ 1 ppm	≤ 1 ppm	≤ 0.005%
Heavy metals	≤ 50 ppm	≤ 50 ppm	—
pH	—	3.8–7.6	—
Mercury	≤ 0.1 ppm	—	—
Peroxides	—	≤ 100 ppm	—
Phenolic preservatives	—	+	—
Gel strength	—	150–250 g	—

# Exhibit 4

## Excipient

From Wikipedia, the free encyclopedia

An **excipient** is an inactive substance used as a carrier for the active ingredients of a medication. In many cases, an "active" substance (such as aspirin) may not be easily administered and absorbed by the human body; in such cases the substance in question may be dissolved into or mixed with an excipient. Excipients are also sometimes used to bulk up formulations with very potent active ingredients, to allow for convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid in the handling of the active substance concerned.

Depending on the route of administration, and form of medication, various excipients may be used. For oral administration, see Tablet and Capsule. For rectal administration see suppository.

Often, once an active ingredient has been purified, it cannot stay in purified form for long. In many cases it will denature, fall out of solution, or stick to the sides of the container. To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time that the shelf-life of the product makes it competitive with other products. Thus, the formulation of excipients in many cases is considered a trade secret.

Pharmaceutical codes require that all ingredients in drugs, as well as their chemical decomposition products are identified and guaranteed to be safe. For this reason, excipients are only used when absolutely necessary and in the smallest amounts possible.

### Contents

- 1 Types of excipients
  - 1.1 Antiadherents
  - 1.2 Binders
  - 1.3 Coatings
    - 1.3.1 Changing the dissolution rates of active species
  - 1.4 Disintegrants
  - 1.5 Fillers/Diluents
  - 1.6 Flavors and Colors
  - 1.7 Glidants
  - 1.8 Lubricants
  - 1.9 Preservatives
  - 1.10 Sorbents
  - 1.11 Sweeteners
- 2 See also

## Types of excipients

### Antiadherents

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and

thus prevent tablet sticking to the tablet punches.

## Binders

Binders hold the ingredients in a tablet together.

Binders ensure that tablets and granules can be formed with required mechanical strength. Binders are usually starches, sugars, cellulose or modified cellulose such as hydroxypropyl cellulose, lactose, or sugar alcohols like xylitol, sorbitol or maltitol.

Binders are classified according to their application:

- Solution binders are dissolved in a solvent (for example water or alcohol and used in wet granulation processes. Examples are Gelatin, Cellulose, Cellulose derivatives, Polyvinyl pyrrolidone, Starch, Sucrose and Polyethylene glycol
- Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples are Cellulose, Methyl cellulose, Polyvinyl pyrrolidone, Polyethylene glycol

## Coatings

Tablet coatings protect tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. For most coated tablets, a cellulose (plant fiber) film coating is used which is free of sugar and potential allergens. Occasionally, other coating materials are used, for example synthetic polymers, shellac, corn protein zein or other polysaccharides.

## Changing the dissolution rates of active species

Enteric coatings or slow release coatings control the rate of drug release, or determine where the drug will be released in the digestive tract.

## Disintegrants

Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. Disintegrant types include:

- Water uptake facilitators
- Tablet rupture promoters

They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution. Examples of disintegrants include: starch, cellulose, crosslinked polyvinyl pyrrolidone, sodium starch glycolate, sodium carboxymethyl cellulose, methylcellulose.

## Fillers/Diluents

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the final product has the proper volume for patient handling.

A good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, soluble, relatively cheap, compactible, and preferably tasteless or pleasant tasting.

Plant cellulose (pure plant filler) is a popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is another popular tablet filler. A range of vegetable fats and oils can be used in soft gelatin capsules.

Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, and, calcium carbonate.

## **Flavors and Colors**

Flavors and Colors are added to improve the taste or appearance of a formulation. Color consistency is important as it allows easy identification of a medication.

## **Glidants**

Glidants are used to improve the flowability of the powder or granules or both.

## **Lubricants**

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and injection can occur with low friction between the solid and die wall.

Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

## **Preservatives**

Some typical preservatives used in pharmaceutical formulations are

- antioxidants like vitamin A, vitamin E, vitamin C, retinyl palmitate, and selenium
- the amino acids cysteine and methionine
- citric acid and sodium citrate
- synthetic preservatives like methyl paraben and propyl paraben.

## **Sorbents**

Sorbents are used for tablet/capsule moisture-proofing by limited fluid sorbing (taking up of a liquid or a gas either by adsorption or by absorption) in a dry state.

## **Sweeteners**

Sweeteners are added to make the ingredients more palatable, especially in chewable tablets such as antacid or liquids like cough syrup. Therefore, tooth decay is sometimes associated with cough syrup abuse. Sugar can be used to disguise unpleasant tastes or smells.

*Exhibit 5*[http://www.epa.gov/opp00001/biopesticides/ingredients/factsheets/factsheet\\_128930.htm](http://www.epa.gov/opp00001/biopesticides/ingredients/factsheets/factsheet_128930.htm)

Last updated on Wednesday, October 31st, 2007.

## Pesticides: Regulating Pesticides

You are here: [EPA Home](#) [Pesticides](#) [Regulating Pesticides](#) [Biopesticides](#) [Active Ingredient Index C, D](#) Chitosan; Poly-D-glucosamine (128930) Fact Sheet

# Chitosan; Poly-D-glucosamine (128930) Fact Sheet

**Issued: 6/03**

### On This Page

- I. [Description of the Active Ingredient](#)
- II. [Use Sites, Target Pests, And Application Methods](#)
- III. [Assessing Risks to Human Health](#)
- IV. [Assessing Risks to the Environment](#)
- V. [Regulatory Information](#)
- VI. [Manufacturers](#)
- VII. [Additional Contact Information](#)

### Related Information

- [Regulating Biopesticides](#)
- [Active Ingredient Index](#)

Information related to this page:

- [Factsheet](#)
- [Federal Register Notices](#)
- [Products](#)
- [Registrants](#)

### Summary

Chitosan is used primarily as a plant growth enhancer, and as a substance that boosts the ability of plants to defend against fungal infections. It is approved for use outdoors and indoors on many plants grown commercially and by consumers. The active ingredient is found in the shells of crustaceans, such as lobsters, crabs, and shrimp, and in certain other organisms. Given its low potential for toxicity and its abundance in the natural environment, chitosan is not expected to harm people, pets, wildlife, or the environment when used according to label directions.

### I. Description of the Active Ingredient

Chitosan (poly-D-glucosamine) is one of the most common polymers found in nature. Structurally, it is related to cellulose, which consists of long chains of glucose molecules linked to each other. In chitosan, the building block of the chains is a slightly modified form of glucose. [For another pesticide active ingredient structurally related to chitosan and cellulose, see [chitin](#), also called poly-N-acetyl-D-glucosamine.] Like chitin, chitosan is present in the shells of all crustaceans and insects, and in certain other organisms including many fungi, algae, and yeast. Commercially, chitosan is prepared from chitin, which is isolated from the shells of crustaceans after the edible parts have been removed.

OPP Chemical Code: 128930 ; (CAS# 9012-76-4)

### II. Use Sites, Target Pests, And Application Methods

- **Use Sites:** Many field crops, ornamentals, and turf grown in fields, home gardens, nurseries, and other sites.
- **Uses:** Plant defense booster; plant growth regulator (enhancer).



# Exhibit 6

Search: ☐ The Web ☐ Tripod[Report Abuse](#)[Previous](#) | [Top 100](#) | [Next](#) »

☆☆☆☆☆

share: [del.icio.us](#) | [digg](#) | [reddit](#) | [furl](#) | [facebook](#)

Hosted



Ads by Google

**2D & 3D Characterization**SEM & TEM tools for materials research & qualification.  
[fei.com/industry](#)**Structured Settlements**Get a Lump Sum Payment for Your Structured Settlement-Free  
Quote[www.StructuredSettlementLumpSum.com](http://www.StructuredSettlementLumpSum.com)

## *Dalwoo-chitoSan*

### Structure of Chitin / Chitosan and Cellulose

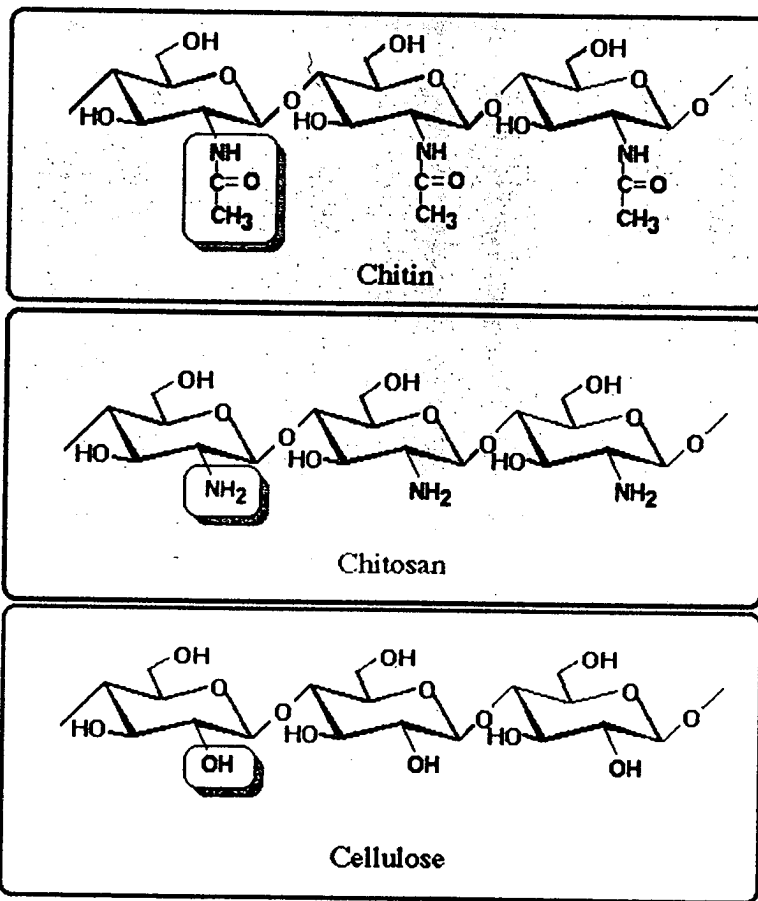


Fig. 3. Structure of Chitin, Chitosan and Cellulose